REVIEW

Renin: friend or foe?

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Renin maintains blood pressure through vasoconstriction when there is inadequate salt to maintain volume. In populations where blood pressure is more often high than low, and vascular death more common than haemorrhage or dehydration, therapeutic reductions in renin secretion or response are valuable. Whether long-term benefits are due entirely to blood pressure reduction remains unproved. The pathway can be blocked at its rate-limiting step (β blockade or direct renin inhibition), the synthesis of the active product, angiotensin II, or at the receptor for angiotensin. Because renin and sodium are the two main factors in blood pressure control, and renin levels vary inversely with sodium load, blood pressure control requires a combination of natriuresis and blocking the consequential increase in renin activity. Being a large and stable molecule, renin is among the easiest and cheapest of hormone measurements. Understanding the simple biochemistry and physiology of renin permits optimal use of the drugs acting to raise or suppress this hormone.

The renin–angiotensin–aldosterone system (RAS) has a central role in acute and chronic regulation of blood pressure (BP). Without renin, blood pressure cannot be protected in the face of sodium depletion.[1] Conversely, in the face of salt loss, excess renin production serves only to maintain, not to increase blood pressure.[2 3] It is in salt-replete humans that renin may be undesirable and contribute both to hypertension and end-organ damage.[4–6] Several classes of drugs have therefore been developed which confer benefit by blocking the effects of renin. Their proven roles are reducing mortality in heart failure and lowering blood pressure in hypertension. Although they also protect against many complications of hypertension, diabetes, vascular and renal disease, critical analysis is required to discern benefits additional to those of blood pressure reduction.

In heart failure, where the physiological compensations can be more harmful than the fall in cardiac output which elicits the compensation, RAS blockade was one of the stunning successes of 20th century medicine. In hypertension, by contrast, RAS blockade has not clearly performed better than other classes of antihypertensive drugs in protecting against the major complications of stroke, coronary heart disease, and (surprisingly) heart failure.[7] This failure can be attributed to the over-riding importance of blood pressure reduction in protecting against complications of hypertension, and to the need for both components of hypertension—salt and renin—to be targeted for blood pressure control to be achieved in most patients.[8] The lesson from heart failure is that the maximum potential of RAS blockade is reaped only when all components of the system are fully blocked in patients in whom RAS would otherwise be maximally activated.[9] This review will describe how this objective can be met in hypertension through an understanding of how RAS responds to physiological and pharmacological manipulation; and illustrate how renin measurements help find the correct drug regimen. Finally, this analysis will permit resolution, or at least explanation, of the controversy surrounding the role of RAS blockade in high-risk patients without overt hypertension or heart failure.

RAS: THE MAIN PLAYERS

Renin is an enzyme secreted from specialised cells in the afferent arteriole of the glomerulus—the "juxtaglomerular apparatus" (JGA). Its circulating substrate, synthesised in the liver, is the protein angiotensinogen, from which renin generates the decapeptide angiotensin I (Ang I). Ang I is in turn converted to the octapeptide Ang II by angiotensin-converting enzyme (ACE) (fig 1A). Ang II is the principal effector molecule of the RAS, whose main actions are to stimulate the AT_1 receptor on arteries and the adrenal cortex to cause vasoconstriction and stimulation of aldosterone secretion. The AT_1 receptor also facilitates noradrenaline release from sympathetic nerves, and has chronic trophic actions promoting growth of muscle cells in the heart and arteries.[4–6] In addition to the classical pathway leading to Ang II and stimulation of the AT_1 receptor, smaller biologically active angiotensin peptides can be formed from Ang I and II, especially when levels of the former are increased during treatment with ACE inhibitors and angiotensin receptor blockers (ARBs).[10] Whereas Ang(2–8) and Ang(3–8) (Ang III and IV) bind to the AT_1 receptors and have similar effects as Ang II, Ang(1–7) binds to the AT_2 receptor and stimulates natriuresis and vasodilatation.[11 12] The role of the AT_2 receptor in adult tissue, however, remains uncertain, being mainly linked to apoptosis of developing tissues during embryogenesis.[13 14]

FACTORS CONTROLLING RENIN RELEASE

Renin secretion from the JGA in the kidney is regulated by four mechanisms: arterial BP, sympathetic nervous system activity, sodium balance and

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Abbreviations: ACEi, ACE inhibitor; Ang I (II), angiotensin I (II); ARBs, angiotensin receptor blockers; BP, blood pressure; CCBs, calcium channel blockers; DRI, direct renin inhibitor; JGA, juxtaglomerular apparatus; PRA, plasma renin activity; RAS, renin–angiotensin–aldosterone system

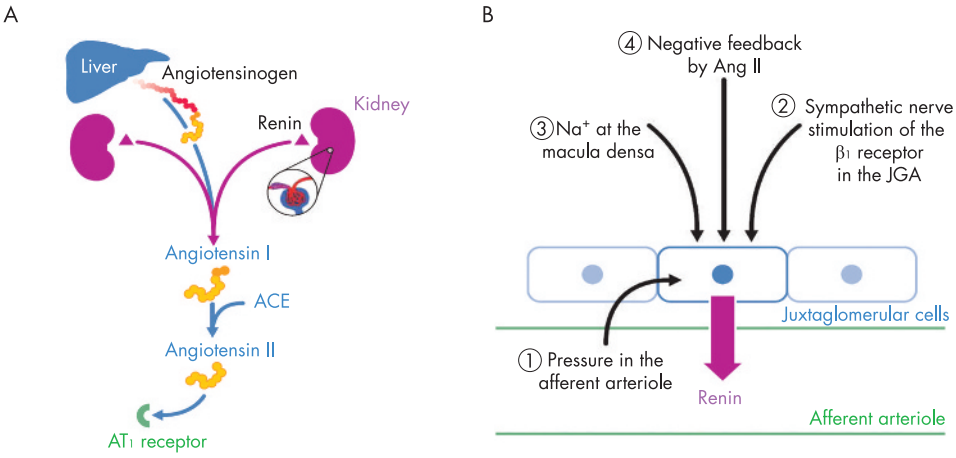


Figure 1 (A) Components of the renin–angiotensin–aldosterone system. (B) The four regulators of renin secretion. JGA, juxtaglomerular apparatus.

negative feedback regulation by Ang II (fig 1B).[15] Interestingly the four major antihypertensive drug classes all cause changes in plasma renin, through one each of these mechanisms.

Pressure[16]: The unusual site of the JGA endocrine secretory cells around arterioles is testament to the importance of pressure sensing in renin regulation. Renovascular hypertension is the classic example of increased renin secretion due to low pressure at the JGA, which senses the post-stenotic pressure and "thinks" that systemic pressure needs to be increased. Renal hypoperfusion in heart failure and hypovolaemic states is responsible for the hyper-reninaemia and consequent secondary hyperaldosteronism in these conditions. Calcium channel blockers (CCBs) and α blockers increase renin partially through their reduction in afferent arteriolar pressure.

Sympathetic stimulation[17]: This is responsible for the two- to threefold increase in renin on standing and exercise, and (through their activation of the baroreceptor) for part of the increase of CCBs and α blockade. The adrenergic receptor on the JGA is the β_1 adrenoceptor—one of the few extracardiac sites of the β_1-subtype—and is coupled to cyclic AMP production, through a specific isoform of adenylate cyclase (type 6).[18] In hypertension, the β blockers work entirely through blockade of renin secretion.[19 20] Side effects due to reduction in cardiac output can be minimised by using the most β_1-selective agents and doses.

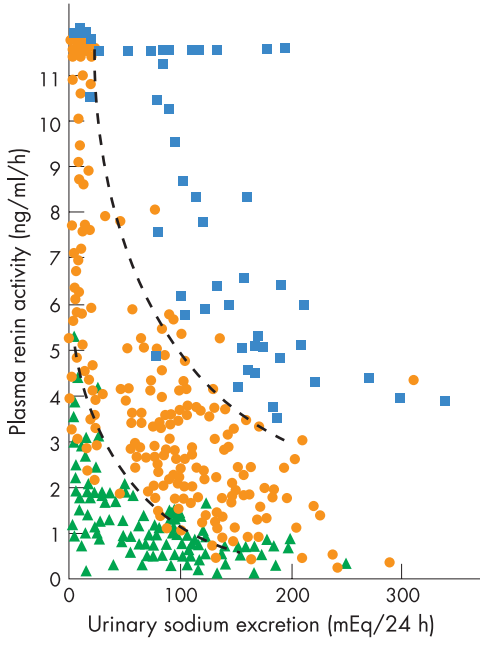


Figure 2 Definition of high, medium, and low renin by renin–sodium profiling.[19] Reprinted with permission from Brunner HR, Laragh JH, Baer L, *et al*. Essential hypertension: renin and aldosterone, heart attack and stroke. *N Engl J Med* 1972;286:441–9. Copyright © 2007 Massachusetts Medical Society. All rights reserved.

Sodium balance[21]: The macula densa cells in the distal renal tubule sense the Na^+ flux through the furosemide-sensitive $Na^+K^+2Cl^-$ transporter. The macula densa is a discrete region of specialised columnar epithelial cells at the point of the renal distal tubule, which lies adjacent to the JGA in the afferent arteriole. Prostaglandins and adenosine act as signals from the macula densa to the JGA, respectively stimulating and inhibiting renin release.[21]

At steady state—that is, when there has been no recent change in sodium intake or output—Na^+ flux at the macula densa is largely a measure of salt intake. Hence the concept of renin–sodium profiles (fig 2), and the major role of dietary salt in determining plasma renin in healthy people.[19] However, the fascinating and clinically important feature of this mechanism is that when Na^+ handling is perturbed either pharmacologically or pathologically, the Na^+ flux through the $Na^+K^+2Cl^-$ transporter and consequent effect upon renin secretion remain altered until the perturbation is removed or corrected. For this reason, as discussed below, measurement of a low plasma renin has become an invaluable method of detecting patients in whom Na^+ retention is present owing to causes such as age-related nephron loss,[22] primary hyperaldosteronism (Conn syndrome),[23] genetic gain of function in a Na^+ channel,[24] or the ingestion of excess salt or a drug which reduces Na^+ excretion.[25] The non-steroidal anti-inflammatory drugs illustrate this last category. Of most practical import, the increase in renin secretion seen with diuretics is due to reduced Na^+ delivery to the macula densa,[26] so that renin measurement allows accurate titration and choice of dose and type of diuretic in patients with resistant hypertension.

Negative feedback regulation by Ang II[27]: The major tonic regulator of renin secretion is through negative feedback regulation by Ang II. Ang II acts via AT_1 receptors on the juxtaglomerular cells to inhibit the release of renin, thus reducing plasma renin activity (PRA) and the production of Ang I and Ang II. Although first recognised in the 1960s, it was only the advent of chronic RAS blockade by ACE inhibitors which led to recognition of the physiological importance of Ang feedback. In most people, ACE inhibitors or ARBs lead to several-fold increases in plasma renin.[28]

The four regulators of renin secretion can amplify or cancel each other. However, most patients receiving β blockade have a low plasma renin, even if also receiving an ACE inhibitor

(ACEi) or ARB.[29] The patients whose PRA remains suppressed despite receiving multiple drugs which stimulate renin secretion must have Na^+-dependent hypertension; this recognition has been invaluable in detecting interesting secondary causes, and in tailoring medical treatment of resistant hypertension.

Age and ethnicity

Sodium balance is the main chronic determinant of individual plasma renin values, leading to considerable interest in surrogates for detecting patients with low renin.[30] Of these surrogates, the main are age and ethnic group. Plasma renin falls by 17% each decade.[31–33] Ethnic variation in renin distribution is also recognised, and in particular younger black subjects have lower levels than Caucasians.[34] There is little doubt that genetic variation in Na^+ handling is the main reason, but none of the genes or alleles has yet been clearly identified; the mechanisms could vary from anatomical variation in nephron number or size to molecular regulation of renal Na^+ channels.

Although the age and ethnic variation in mean renin levels is striking, it is important to emphasise individual variation[35 36]; no sudden transition to low-renin hypertension occurs once patients enter their later 50s and 60s. Now that we recognise the importance of determining a patient's place in the spectrum of plasma renin in order to rationalise treatment, there is a case for measuring rather than guessing the renin level from the surrogates of age and race. As will be discussed, renin measurement may be especially helpful in treated patients, where the effects of treatment move patients across the spectrum.

MEASURING RENIN SYSTEM ACTIVITY

Terminology

"Renin activity" measures the capacity of renin to generate Ang I. "Renin mass" refers to the amount or concentration of renin (not including its precursor, prorenin) in the plasma. "Active renin" was formerly used to describe the amount of renin in the plasma.

Renin assays

PRA assays measure by competitive radioimmunoassay the amount of Ang I generated in a 1 hour incubation of plasma.[37]

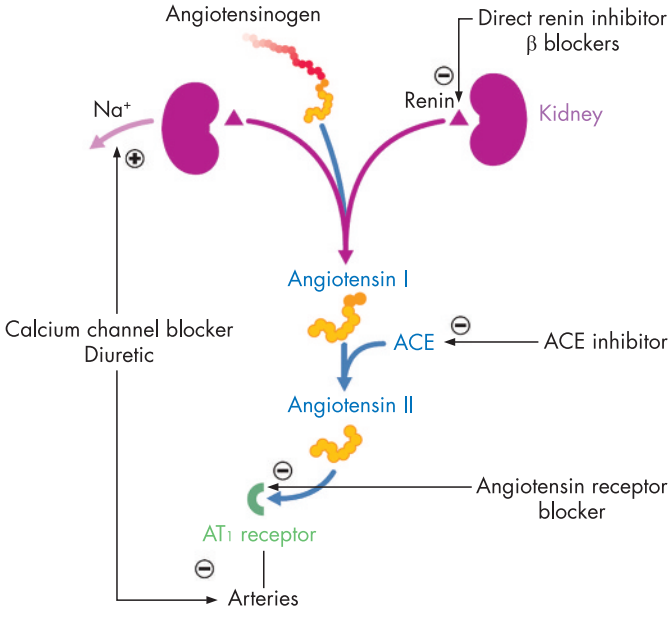


Figure 3 Effects of the main classes of antihypertensive drugs upon the renin–angiotensin system.

The enzymatic amplification generates a sensitive assay, but at the expense of the labour required to measure each sample with and without the hour's incubation. When PRA is low, there is little amplification, and the log-normal distribution of renin means that a disproportionate number of samples are below detection limits.[29] Because the assay relies on the presence in plasma of saturating levels of renin substrate (ie, angiotensinogen), very high renin levels can be underestimated as a result of substrate exhaustion before the hour's incubation is complete.

Renin mass is measured by a two-site (or "sandwich") assay.[38 39] An immobilised antibody that binds both renin and prorenin is used to capture enzyme from the sample. Renin is then measured using a second, labelled antibody specific to renin. Chemiluminescent labelling has enabled cheap, high-throughput and highly sensitive ELISA plate assays, which extend the limits for renin detection at both ends of the range.

The observation, with the newer assays, that renin concentration varies up to 1000-fold between subjects, compared with the trivial two- to threefold within-subject changes with posture and exercise, supports a more important chronic rather than acute role for renin (the reverse is probably true of the sympathetic system). The observation also has a valuable practical import, telling us that random outpatient samples from seated patients are perfectly adequate for detecting patients with abnormal values at either end of the range.[29] In other words, we can distinguish the patient with "high renin" and "low renin" without bringing them into hospital, as used to be taught, for a night of rest before sampling! Moreover, renin is stable in blood for several hours, provided that the sample is not chilled (to avoid cryoactivation of the prorenin to give spuriously high renin values).[40 41]

CLINICAL RELEVANCE OF PLASMA RENIN MEASUREMENTS

Because of the textbook teaching that accurate renin assessment required admission to hospital, and the expense of older assays, renin measurements have typically been reserved for research or specialist investigation. The principal clinical value of renin measurement, historically, has been the recognition of patients at the upper and lower extremes of the distribution who may have secondary causes of hypertension—particularly renal artery stenosis (high renin) and primary hyperaldosteronism (Conn syndrome: low renin). A less well known use of renin measurement is in the assessment of patients with *low* blood pressure. Here the initial differential usually lies between an autonomic neuropathy, where loss of sympathetic innervation of the JGA β_1 receptor leads to profound renin suppression, and Na^+ depletion, where a combination of macula densa and adrenergic stimulation causes a marked increase in renin levels.

Renin measurements have also been of interest in epidemiology, where the recently confirmed evidence that high renin is an independent risk factor for myocardial infarction led to placebo-controlled trials like HOPE investigating the benefit of RAS blockade in high-risk patients, and to the hypothesis of benefits from RAS blockade "beyond blood pressure control".[36 42 43] To date, the complexity of the older renin assays has limited the number and size of epidemiological studies measuring renin, with the consequence that its predictive value in individual patients remains controversial and probably small.[43 44] The high-throughput renin mass assay provides an opportunity for incorporating measurements into adequately powered prospective studies.

However, the main large-scale clinical potential of automated renin assays is in the rationalisation of drug treatment for hypertension, as well as more efficient detection of patients with secondary causes. Samples taken from a patient seated for 10–15 minutes are adequate for interpretation. It is generally

Table 1 Impact of different classes of antihypertensive agent on renin mass and plasma renin activity

Treatment	Renin mass	PRA	Ang I	Ang II
ACE inhibitor	↑ ↑ ↑	↑ ↑ ↑	↑ ↑ ↑	↓ ↓
ARB	↑ ↑ ↑	↑ ↑ ↑	↑ ↑ ↑	↑ ↑ ↑
β Blocker	↓ ↓	↓ ↓	↓ ↓	↓ ↓
CCB	↑	↑	↑	↑
Diuretic				
Thiazide	↑	↑	↑	↑
K^+-sparing	↑ ↑	↑ ↑	↑ ↑	↑ ↑
DRI	↑ ↑ ↑	↓ ↓	↓ ↓	↓ ↓

ACE, angiotensin-converting enzyme; Ang, angiotensin; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DRI, direct renin inhibitor; PRA, plasma renin activity.

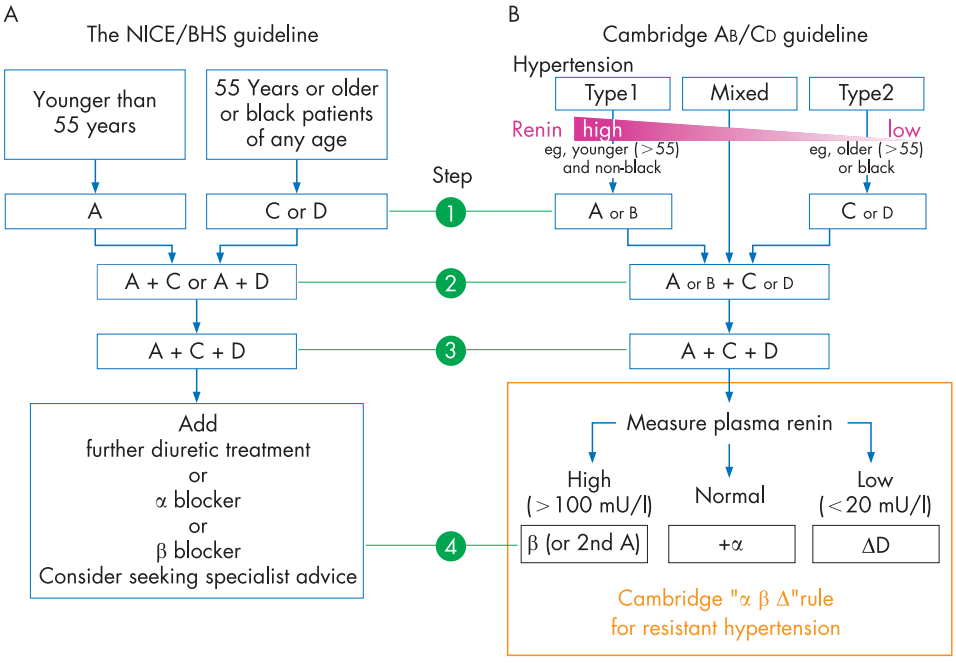
unnecessary to change treatment, provided that the effects of drugs are borne in mind, as summarised below. Although blood samples for renin can be taken in the primary care setting—and we ourselves conduct much of our research there,[29] and routinely request renin sampling before patients' first clinic visit—renin should probably remain a specialist measurement until there is good evidence of benefit from more widespread use.

Influence of treatment on plasma renin and other components of RAS

All drugs in use for hypertension have an influence on plasma renin and other components of RAS (fig 3).[29 45] In the case of "B, C, D" drugs, the change in plasma renin reflects the change in overall RAS activity—suppressed by β blockers ("B"), activated by CCBs ("C") and diuretics ("D") in compensation for their reduction of BP and Na^+ excess. The "A" drugs, by contrast, act like "B" to suppress RAS, but cause an increase in renin secretion by blocking the negative feedback of Ang II upon renin (table 1). Whether this increase in renin and consequently Ang I levels can lead to escape from ACE inhibitors and/or ARBs remains uncertain. Interestingly, the increase in renin mass is probably the best "downstream" measurement of the RAS pathway because the more effective the blockade, the greater the loss of negative feedback. Plasma renin rises more on treatment with a combination of an ACE inhibitor and an ARB than with either alone, indicating that neither alone is maximal.[28] The recently introduced class of direct renin inhibitor (DRI) also blocks the negative feedback, but causes a dissociation between the rise in renin mass and reduction in renin activity (table 1).[46] Plasma levels of Ang (both I and II) fall on β blocker and DRI treatment,[46 47] whereas they are dissociated on ACEi treatment (high Ang I, low Ang II) and increased on ARB treatment. Aldosterone is a variable downstream marker of RAS activity, because even slight increases of its major secretagogue, K^+, can over-ride the expected reduction owing to RAS blockade.

HOW TO SELECT TREATMENTS: IMPACT OF RENIN UPON CURRENT GUIDELINES

That hypertension must be due to either or both of excess vasoconstriction and volume is as incontrovertible as the law of



A: ACE inibitor or ARB
B/β: β blocker
C: Calcium channel blocker
D: Diuretic (thiazide and thiazide-like)
α: α blocker
Δ: Change drug or dose (of diuretic)

Figure 4 Treatment algorithms based on recognition of renin and Na^+ as the two key players in hypertension. (A) The NICE/BHS Guideline.[49] This is based on the original AB/CD rule,[20] but β blockade is dropped as a first-line option except for special cases. The guideline is for the treatment of patients with uncomplicated disease, and is aimed at primary care doctors. (B) A modification of the AB/CD rule, for the specialist treatment of hypertension. This extends the renin–Na^+ rationale of treatment to include a new "α, β, Δ" rule for the treatment of patients with resistant hypertension. Renin measurements may also be an improvement on the surrogates of age and ethnicity for the initial choice of treatment.

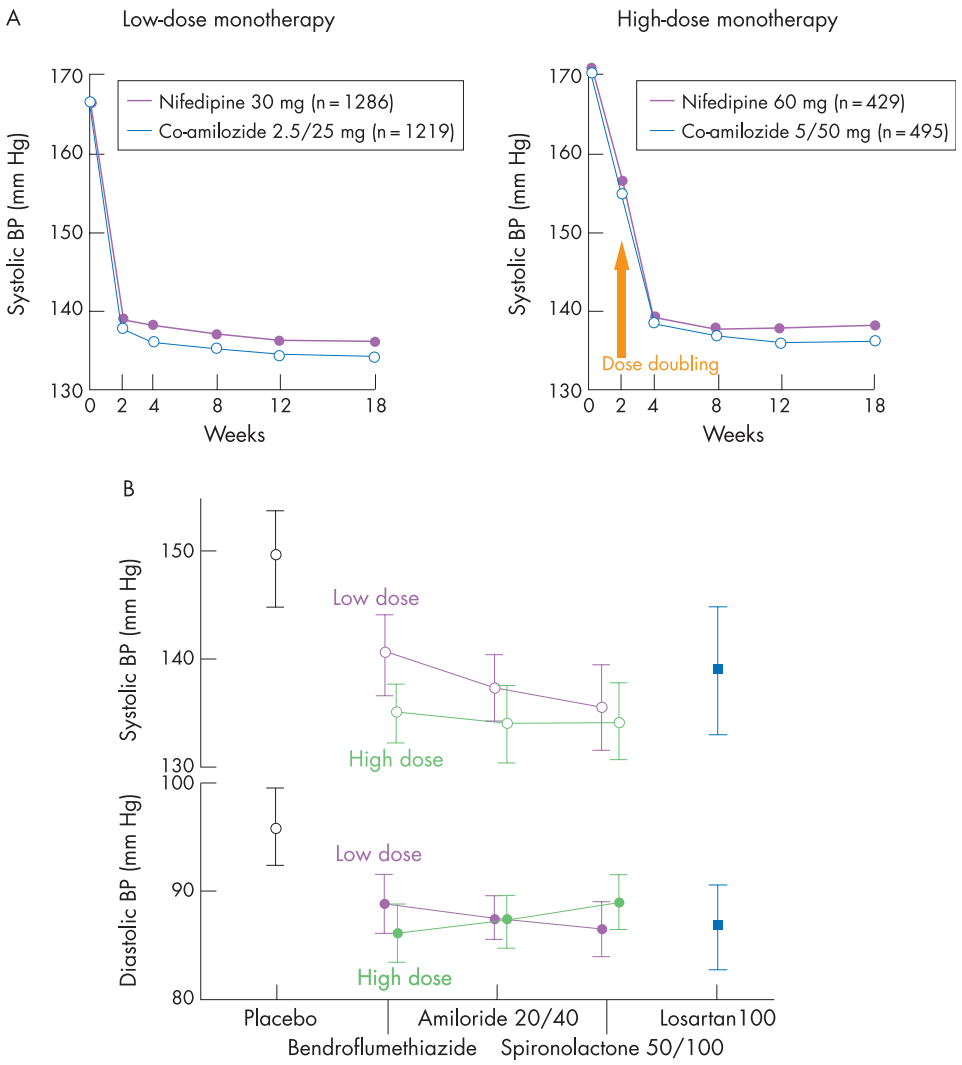


Figure 5 Low-dose thiazides are not maximal. (A) Comparison of hydrochlorothiazide 25 mg and 50 mg in the INSIGHT Trial.[81] A total of 6321 patients with hypertension were randomised, after a month receiving placebo alone, to double-blind treatment with *either* hydrochlorothiazide 25 mg + amiloride 2.5 mg (co-amilozide) *or* nifedipine gastrointestinal therapeutic system 30 mg daily. Further doses of drugs were added in patients remaining above target blood pressure (140/90 mm Hg). Blood pressure (BP) is shown, during the titration phase of the trial, for those patients who continued to receive low-dose monotherapy throughout (left panel) or had their dose of randomised treatment doubled at 2 weeks (right). (B) Comparison of bendroflumethiazide 2.5 mg and 5 mg and other diuretics.[82] Fifty-seven patients with low-renin hypertension received, in random order, placebo, losartan, and two doses of the three diuretics shown, each for 5 weeks. Bendroflumethiazide 5 mg was 5/2 mmHg more effective than 2.5 mg ($p = 0.005$) in lowering BP.

physics—Poiseuille's law[i]—from which the assertion is derived. That renin is the major chronic vasoconstrictor was suggested long ago, but remains a conjecture based on the difficulty of maintaining blood pressure during salt depletion after RAS blockade, and the absence of new vasoconstrictor candidates from the genome project. That all successful drugs for hypertension work primarily through either RAS blockade or Na^+ elimination is also still a theory, based partly on studies comparing the same patient's response to the major drugs, and partly on the failure of drugs blocking alternative pathways (eg, the sympathetic) to achieve similar efficacy in BP reduction.

The concept of two types of hypertension, each with their preferred initial treatment, is now enshrined in the NICE and BHS treatment guidelines.[48] (fig 4A). Based on the original AB/CD algorithm,[20] these recommend "A" (exceptionally "B") for younger Caucasians, and "C" or "D" for all others. However, the guidelines also recognise that most patients should have a combination of the two pairs, given that most patients do not lie at the extremes of plasma renin, and need both vasoconstriction and volume components to be blocked. Recent outcome trials have, indeed, reported an average of more than two drugs per patient once target BP is achieved. At present all guidelines, except the American (JNC 7)[49] recommend initial treatment with monotherapy. But the failure of the less well controlled BP in one arm of the VALUE[50] and ASCOT[51] studies to "catch up", despite more add-on treatment eventually being used in that arm, has raised the interesting possibility that monotherapy stimulates overcompensation, from the component of hypertension that is not blocked (vasoconstriction or Na^+ retention). Studies are planned, therefore, to determine the idea that initial combination therapy should be the norm in most patients.[52]

Treatment guidelines: evidence and details

Evidence for the AB/CD approach came initially from two crossover studies, which examined the effects of multiple antihypertensive treatments in younger patients (<55 years) rotated through the main classes of antihypertensive agents: ACE inhibitor (A), β blocker (B), CCB (C) and diuretic (D).[20 53] Patients were almost twice as responsive to ACE inhibitors or β blocker treatment as to a CCB or diuretic. The exceptions were either in the oldest patient quartile or those who had the lowest PRA, consistent with previous studies.[54 55] In both crossover studies, the correlation between responses to the different pairs of treatments was only strong between A and B (ie, patients who responded to A also responded to B), and between C and D. Small crossover studies do not usually influence NICE guidelines. However, AB/CD correctly predicted the poorer BP

[i]Jean-Louis Marie Poiseuille (1799–1869): Laminar flow down a rigid tube is proportional to the pressure difference between the ends. Better known to cardiologists for his subsequent recognition that the proportionality constant includes the tube's radius raised to the fourth power: $R = \pi r^4 p/8\eta l$

control, and therefore outcome, in older patients receiving an ''AB'' drug in each of VALUE, ASCOT and ALLHAT.[50 51 56]

The main difference between the NICE/BHS 2006 guideline and the original AB/CD rule is the demotion of ''B'' to special indications. This was a response to the higher stroke rates with atenolol treatment in recent trials, particularly when compared with ''A'' in the LIFE study.[57] Interestingly, this unexpected result may also be explained by one of the crossover studies, which reported a threefold increase in both augmentation index—the now popular measure of arterial wave reflection from a stiffened aorta—and plasma B-type natriuretic peptide during β blocker treatment.[58 59] This adverse effect was confirmed in the atenolol group of the CAFE substudy of ASCOT.[60] The diabetogenic effect of ''B'' has also been blamed, but the similar effect of thiazides is less clearly harmful, and the long-term consequence of new-onset diabetes in patients receiving ''B'' or ''D'' remains to be resolved.

From guidelines to practice

Although the mass of outcome data and their meta-analysis in hypertension is perhaps unique in medicine, it is ironic that we are left with a smaller choice of first-line drugs than a decade ago when the studies were planned. If, however, there are only two physiological routes to developing hypertension, it was inevitable that we would eventually recognise only two main categories of drugs. Within these categories we still have some genuine choices to help cope with patients who do not tolerate or respond to the first choices. There are two classes of ''A''; and with excellent timing the renin inhibitor class has arrived as a potential replacement for ''B'', acting at the rate-limiting step of RAS, but expected to lack the downsides of ''B'' owing to extrarenal β blockade.[61 62] Within ''CD'', we have several classes of diuretics other than thiazides. But the reason why an understanding of the renin system is important, and the availability of cheap measurement so exciting, is that it is now both necessary and possible to adopt an efficient, rational approach to optimising the choice of drug(s) and doses from the two categories of drugs.

If understanding renin helps us to understand the evidence underpinning the guidelines, the understanding is even more important in progressing beyond where NICE/BHS left off because of lack of evidence. Figure 4B illustrates, pending further evidence, a strategy of using renin rather than rote to guide treatment choice at any stage in management. Poiseuille's law holds, whether or not a patient has started medication, but the patient's place in the renin spectrum may shift with treatment. For instance, RAS activation by diuretic may convert a volume-dependent patient to a renin-dependent patient, in whom a combination of RAS blockers becomes worthwhile. Conversely, the relief of renin-driven vasoconstriction may reduce pressure natriuresis, and convert a vasoconstricted-patient to a volume-dependent patient requiring higher doses of thiazide or combination with other diuretics. In theory, at least, even the most difficult hypertension should yield to a combination of sufficient RAS blockade and diuretic.

Diuretic choice and dose in low-renin hypertension

Choice of diuretic and dose may sound obvious but this was ignored for years in the development of fixed-dose combinations of thiazide, usually HCTZ 12.5 mg, with various RAS blockers: β blockers, ACEi and, till recently, ARBs. The view that low-dose thiazide is maximal came from small parallel-group studies of untreated, often younger patients (ie, those with high renin).[63 64] The older patient, as we have seen, typically has low renin and requires combination treatment. Figure 5A shows the dramatic effect of doubling even a 25 mg dose of HCTZ in several hundred patients, aged 55–80, randomly assigned to ''C'' or ''D''. And in a recent crossover study of patients with low renin despite treatment with a CCB, we found that a dose of bendroflumethiazide 5 mg was necessary to achieve the same BP reduction as spironolactone 50 mg or amiloride 20 mg (fig 5B). ''The ''de-suppression'' of plasma renin by bendroflumethiazide was also dose related, but even at 5 mg bendroflumethiazide was only half as effective as the K^+-sparing diuretics in increasing renin. So in patients with resistant hypertension—uncontrolled despite use of A + C + D—the value of adding spironolactone or amiloride is due partly to natriuresis, but partly also to their renin activation and hence potentiation of the RAS blockade. Currently we use spironolactone only in such resistant patients.[29 65 66] For first-line treatment we use thiazides, sticking to low doses to avoid diabetes, with a ''whiff'' of amiloride to avoid hypokalaemia.[67] Perhaps it would in the future be more logical to use an effective dose of amiloride or spironolactone to avoid diabetes, with a ''whiff'' of thiazide to avoid hyperkalaemia. Outcome data may be lacking, but we also lack outcome data to support the benefits of thiazides at their currently recommended doses.

Treatment combinations for patients with high renin, and their titration

Once patients are receiving multiple diuretics and a CCB, they resemble another condition associated with very high renin levels—namely, heart failure—in which a combination of multiple RAS blockers has been shown to be beneficial.[9] However, as mentioned earlier, a downstream demonstration of complete RAS blockade is difficult with most of the drugs. Plasma aldosterone is affected by small rises in K^+, and plasma Ang II is either unmeasurable or unmeaningful after ACEi or ARB treatment, respectively. Dose-related changes in renin activity or Ang II can be demonstrated after β blockade or DRI, and show that the latter reduces PRA even when combined with the drugs that normally increase PRA.[68]

Tissue renin

This article has concentrated on circulating renin because it is measurable and explains most of the observed effects of the drug classes discussed. Local production within the heart, arteries and kidneys is likely, but its importance is much harder to ascertain than that of circulating renin.[15] That may change with the discovery of a ''renin receptor'' in these tissues, which binds both renin and its precursor, prorenin, causing non-proteolytic activation of renin system activity with production of Ang I and the activation of intracellular mitogen-activated protein kinases, ERK1 and ERK2, independently of angiotensin production.[69 70] Blockade of the non-proteolytic activation of prorenin by a decoy peptide inhibits the development of left ventricular fibrosis and hypertrophy in stroke-prone spontaneously hypertensive rats.[71] These are early and exciting days in our unravelling of the renin receptor, and determination of whether it provides another target to be considered in achieving full RAS blockade.

BENEFITS BEYOND BP CONTROL?

One of the reasons for interest in tissue renin is as an explanation for the still controversial notion that RAS blockade confers outcome benefits not explained by BP reduction alone.[72] This seems most widely accepted, if still not completely proved, in the treatment of diabetes and some other nephropathies, with some evidence also for benefit of combined RAS blockade to reduce proteinuria.[73] For more major complications of hypertension, the most up to date retrospective meta-regression analysis of data from almost 150 000 patients provides some encouragement, reporting that ACE inhibitors achieve BP-independent reduction in the relative risk of coronary heart disease of about 9% (95% CI 3 to 14%).[74] In trying to dissect this observation, it is tantalising that in support of the strictest

Key points

- The main physiological role of the renin–angiotensin system (RAS) is to protect against Na^+ loss, and the hypotension which results. When inappropriately high for the level of Na^+ in the body, renin production can contribute to hypertension and end-organ damage.
- Renin secretion is regulated by four mechanisms: arterial pressure, sympathetic nervous system activity, salt intake and negative feedback regulation by Ang II.
- Most antihypertensive drugs influence the measurement of plasma renin activity (PRA), acting on one of the above mechanisms. ACE inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers and diuretics increase PRA, whereas β blockers and renin inhibitors reduce PRA.
- At the population level, PRA is negatively correlated with age and Na^+ intake, and therefore also with blood pressure (BP). In many patients with hypertension, however, PRA is inappropriately high for the level of Na^+ intake, and limits the effectiveness of drugs used to eliminate Na^+.
- In hypertension, therefore, it is rational to combine drugs which, respectively, eliminate Na^+ and block the RAS. Combination treatment is likely to become routine even for initial treatment of most patients, and will improve rates of BP control.
- In high-renin states—namely heart failure, strategies to increase RAS suppression (eg, ACE inhibitor/ARB combination therapy) can improve treatment outcomes. In other conditions, benefits are proportional to the prior contribution of renin to a patient's hypertension or other cardiovascular risk.
- Measurement of renin is now straightforward. In addition to diagnosis of secondary causes of hypertension, the measurement permits recognition and titration of the patient with low renin in whom extra diuretic is required to de-suppress renin secretion and potentiate further RAS blockade.

interpretation of the hypothesis, a number of ACE inhibitors have demonstrated outcome benefit for patients with *controlled blood pressure,* despite blood pressure falls of <5 mm Hg.[42 75 76] In similar *normotensive* populations, calcium blockers have not achieved benefit[76]; and meta-analysis of ''more versus less'' BP lowering in uncontrolled hypertension shows benefit of ''intensive'' BP control only in patients with diabetes.[77] But in prospective analyses the RAS hypothesis remains not so much unproved, as untested, because of the failure closely to match BP between groups.[74 78–80] As this article has now explained, the failure was inevitable because of the age-related fall in renin, and change in pattern of BP response. To test the RAS hypothesis, renin needs first to be de-suppressed by ''C'' or ''D'', as now recommended for first-line treatment of older hypertensive patients,[48] and a pilot study conducted to match BP on the selected RAS-blocking and non-blocking regimens.

CONCLUSION

So, renin: friend or foe? Given the number of drug classes we employ to block renin, it is certainly seen mainly as foe. For middle-aged and older populations eating Western diets rich in salt and fat, renin may indeed be at best unnecessary and at worst harmful. Yet in the contest between renin and Na^+ which, as this article has explained, underpins hypertension, it is Na^+ which wins in Western society, leading to suppression of renin secretion from ageing kidneys. So when it came to the large outcome trials in older hypertensive patients comparing drugs which targeted renin or Na^+ as their primary mode of action, the latter have generally outperformed simply by lowering BP more effectively.

These trials teach us that we should use renin as a friend in order to reap maximum benefit from RAS blockade. This means rendering hypertension renin-dependent by optimal use of diuretics, and by measuring renin to help determine when more diuretic or more RAS blockade is required. Despite considerable progress in the past decade, most patients with hypertension have failed to achieve target BP, and we have failed to ascertain the true benefits of renin blockade. Rational understanding and exploitation of the renin–salt interaction allows these failures in the clinic and research to be reversed.

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